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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,476	02/27/2002	Raffaele De Francesco	IT0002PCA	5843
210	7590	02/24/2004	EXAMINER	
MERCK AND CO INC P O BOX 2000 RAHWAY, NJ 070650907			HUTSON, RICHARD G	
			ART UNIT	PAPER NUMBER

1652

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/085,476

Applicant(s)

DE FRANCESCO ET AL.

Examiner

Richard G Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-19 is/are pending in the application.
- 4a) Of the above claim(s) 8-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2/2002.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Claims 8-19 are still at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group II, Claims 12-19, in the paper of 1/20/2004, is acknowledged.

Claims 8-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Applicants amendment of the first line of the specification to state that "The present application is a continuation of the U.S. Application No. 08/952,981, filed March 23, 1998, which is the U.S. national filing of PCT/IT96/00106, International filing date May 24, 1996 (published in English)." is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

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Those references considered, listed on the 1449 submitted with the information disclosure statement of 2/27/2002, have been initialed.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 12, 14, 16, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Behrens et al. (EMBO 15(1): 12-22, January 1, 1996).

Behrens et al. teach the identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus as that protein encoded by the NS5B protein. Behrens et al. teach the expression of the NS5B protein, ribonucleotide substrates and a RNA template to produce RdRp and TNTase activity. The NS5B protein which corresponded to the amino acid sequence of SEQ ID NO: 1 was purified by Behrens et al.

One of ordinary skill in the art at the time of filing would have been motivated to modify the method taught by Behrens et al., by adding test compounds, to identify and measure the ability of compounds to affect hepatitis NS5B activity, both RdRp and TNTase as a means of identifying potential therapeutics against hepatitis C virus. The reasonable expectation of success would be that the identification of proteins that inhibit

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NS5B activity, a necessary activity for the propagation of hepatitis C virus, would also inhibit the propagation of hepatitis C virus.

Thus, Behrens et al. makes obvious claims 12, 14, 16, 17 and 18. As discussed above, it is noted that the date of publication of the Behrens et al. reference is prior to the date of filing of the PCT application but after the claimed priority document and thus this rejection can be overcome by the filing of a translation of the claimed priority document.

Claims 12, 14, 16, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Al et al. (Hepatology 22(4 part 2): 331A, October 1995).

Al et al. teach the expression and characterizations of the NS5B (RNA-dependent RNA polymerase) gene of hepatitis C virus. Al et al. teach the expression of the NS5B which corresponds to the amino acid sequence of SEQ ID NO: 1 was purified by Al et al. Al et al. also teach that specific compounds (nucleoside analogues) that inhibit this enzyme in vitro may prove to be useful in treating patients with chronic hepatitis C virus infections.

One of ordinary skill in the art at the time of filing would have been motivated to use the method taught by Al et al. to combine the NS5B protein, ribonucleotide substrates, and a RNA template and test compounds, to identify and measure the ability of a compound to affect hepatitis NS5B activity, specifically RdRp activity as a means of identifying potential therapeutics against hepatitis C virus. Al et al. suggest the motivation for such methods in their teaching that specific compounds (nucleoside

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analogues) that inhibit this enzyme in vitro may prove to be useful in treating patients with chronic hepatitis C virus infections. The reasonable expectation of success would be that the identification of proteins that inhibit NS5B activity, a necessary activity for the propagation of hepatitis C virus, would also inhibit the propagation of hepatitis C virus.

Thus, Al et al. makes obvious claims 12, 14, 16, 17 and 18. As discussed above, it is noted that the date of publication of the Al et al. reference is prior to the date of filing of the PCT application but after the claimed priority document and thus this rejection can be overcome by the filing of a translation of the claimed priority document.

Claims 12, 14, 16, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al. (Journal of Virology 67(7): 4017-4026, July 1993).

Tomei et al. teach that the Hepatitis C virus (HCV) is considered to be the major etiologic agent of post-transfusion non-A, non-B hepatitis and that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa. Tomei et al. also teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5). Tomei et al. further teach DNA constructs and transient expression of the HCV genome and characterize the post-translational processing of the HCV transcript, and specifically transcribe and

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translate NS5B, described by SEQ ID NO: 1. (see page 4020, Figure 1 and also Figure 3A).

One of ordinary skill in the art at the time of the filing of the invention would have been motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase, wherein said incubation takes place *in vitro* in order to further characterize the function and role of the protein(s) encoded by the NS5B ORF. The expectation of success comes from the high degree of skill in the art with respect to protein expression, as demonstrated by Tomei et al. in their expression of the HCV cDNA encoding the entire polyprotein using a vaccinia virus T7 expression system. One of ordinary skill at the time of invention would have been motivated to produce the NS5B protein both by the independent transcription and translation of the NS5B as well as by the proteolytic processing of the NS2-NS3-NS4-NS5 polyprotein to determine if the proteolytic processing event affects the activity of the NS5B protein product. One would have been further motivated to vary the RNA templates and primers in the incubation mixture to characterize the specific mechanism of action of any RNA-dependent RNA polymerase activity. The motivation for the addition of ribonucleotide substrates and a RNA template comes from the suggestion by Tomei et al. that the NS5B encodes a RNA-dependent RNA polymerase. The reasonable expectation of success comes from the teaching of Tomei et al. that while the nonstructural region of the HCV genome has not been characterized in detail, it is thought to be processed in a manner similar to that of flaviviruses and pestiviruses and the hydropathy profile of HCV polyprotein is similar

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to that of the flavivirus polyprotein as well as the suggestion that the NS5B ORF encoded protein is a RNA-dependent RNA polymerase. One of ordinary skill in the art at the time of filing of the application would have been further motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase activity, wherein said incubation takes place *in vitro* in the presence of potential target molecules which may inhibit the action of the NS5B protein as a means of identifying potential therapeutics to be used against the NS5B protein and HCV. The motivation for why one of skill in the art would be interested in the function of the NS5B ORF is because as one of only a few HCV encoded nonstructural proteins the protein(s) encoded by the NS5B ORF is a prime target for the development of therapeutics against HCV. A reasonable expectation of success comes from the high degree of knowledge in the art with respect to protein expression and the identification of inhibitors of said proteins activity, as discussed above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12, 14, 16, 17 and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S.

Patent No. 6,383,768. An obvious type double patenting rejection is appropriate where conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 8-15 of U.S. Patent No. 6,383,768 drawn to a method for measuring the ability of a compound to affect hepatitis C virus (HCV) NS5B activity comprising: (a) incubating in vitro a composition comprising HCV NS5B, ribonucleotide substrates, an RNA template, and said compound, under conditions suitable to produce NS5B RNA-dependent RNA polymerase activity, wherein said NS5B is provided to said composition from a preparation wherein said NS5B is the only HCV protein present and (b) measuring the ability of said compound to affect said NS5B RNA-dependent RNA polymerase activity anticipates claims 12, 14, 16, 17 and 18 of the instant application.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to

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identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 13, 15 and 19 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 8, 15 and 11 of prior U.S. Patent No. 6,383,768. This is a double patenting rejection.

Remarks

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', with a horizontal line extending to the right.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rg
2/20/2004